SCIENTIFIC ABSTRACT

The primary objective of this study is the assessment of the safety of intramuscular administration of a recombinant adeno-associated virus 1 (rAAV1)-alpha 1 antitrypsin (AAT) gene vector in AAT deficient adults. The secondary objective is to determine the dose of rAAV1-CB-hAAT vector required to achieve a detectable level of normal M-variant AAT in AAT-deficient adults.

A recombinant virus vector constructed from adeno-associated virus (AAV) has been altered to carry the human alpha-1 antitrypsin (hAAT) gene expressed from a hybrid chicken beta actin promoter with a cytomegalovirus enhancer. The construct has been shown to initiate the production of hAAT in laboratory animals. The proposed human clinical trial is an open label, Phase I study administering rAAV1-CB-hAAT gene vector, at a single dose per subject, and dose escalated between each of four (4) cohorts of three (3) subjects. Gene expression in blood samples can be measured directly by ELISA to assess safety.

Administration is by intramuscular injection, at three separate sites, of approximately 1.5 ml each (total of 4.5 ml) in the deltoid muscle of the non-dominant upper extremity (left arm for right-handed subjects) with ultrasound guidance to avoid large vascular structures. The regimen is a single administration consisting of one session of injections. Doses of vector will range from 2.1×10^{12} to 7.0×10^{13} vector genomes (vg) per subject, which corresponds to approximately 3×10^{10} to 1×10^{12} vg/kg.

Safety endpoints to be assessed are: serum hAAT (11 micro molar is the lower limit of the therapeutic range); and, changes in hematology, urinalysis, pulmonary function, semen assay for vector genomes, immunologic response to AAT and AAV, and reported history of any symptoms.

Any subjects currently on AAT replacement therapy will discontinue AAT protein replacement four (4) weeks prior to receiving their vector dose, resuming 11 weeks after the dose has been administered.